**InKine Pharmaceutical Company, Inc.**

**MARTIN ROSE, M.D., J.D.**
*Senior Vice President*
*Clinical Research & Regulatory Affairs*



April 27, 2000

Dockets Management Branch
United States Food and Drug Administration
HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20857

**Re: Docket No. 78N-036L**

Dear Madam or Sir:

I am writing on behalf of InKine Pharmaceutical Co., Inc (InKine), in response to a letter to Lilia Talarico, M.D., from Jack DiPalma, M.D., dated December 10, 1999. In that letter, Dr. DiPalma raised concerns about the safety of sodium phosphate bowel preparation products. The letter was placed on FDA's Dockets Web site (Docket No. 78N-036L) and is now available to the public. InKine is the manufacturer of Diacol™ Tablets (sodium phosphate monobasic, monohydrate and sodium phosphate dibasic, anhydrous), an investigational colon cleansing agent. We have several serious concerns regarding Dr. DiPalma's letter:

- We disagree strongly with Dr. DiPalma's conclusions regarding the risks of sodium phosphate products. His views are contrary to FDA's own published conclusions regarding the excellent safety record of sodium phosphate when it is used as directed.

- Dr. DiPalma failed to disclose his conflict of interest arising out of his role as a "medical director/consultant" of Braintree Laboratories, Inc (Braintree), a manufacturer of bowel preparations that compete with sodium phosphate.

First, in his conclusions regarding the risks of sodium phosphate products, Dr. DiPalma has ignored the weight of the evidence and FDA's own exhaustive review of this issue. In a series of lengthy Federal Register notices relating to an official FDA Docket (No. 78N-036L), FDA carefully analyzed the available information regarding the safety of sodium phosphate, including the published literature and FDA's own adverse event



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database. FDA's review focused closely on electrolyte changes that may occur in patients taking sodium phosphate, and considered Dr. DiPalma's study regarding the safety of sodium phosphate that he referenced in his letter. Notably, Braintree on several occasions contributed information to this Docket. After considering all of the data regarding the sodium phosphate solution, FDA concluded that:

"The agency has not received any reports that a one-time 90 mL dose has resulted in a death or a serious adverse reaction requiring medical attention." [1]

Dr. DiPalma should have been aware of FDA's conclusion, because he has contributed to the Docket, as has Braintree on several occasions. Dr. DiPalma's letter fails to mention the results of FDA's review of the data, or even that FDA performed a review.

Note that in the professional labeling for sodium phosphate solution, the recommended total dose of sodium phosphate solution for colon cleansing is 90 mL. This indicates that FDA has determined that sodium phosphate solution is safe when used as directed for colon cleansing. Oral sodium phosphate solution has been marketed in the United States for over 100 years, and in recent years it has been used by about 1 to 2 million persons yearly as a bowel preparation prior to colonoscopy and related procedures. [2] We estimate that more than 10 million persons have used oral sodium phosphate solution as a bowel preparation. This vast experience indicates that when sodium phosphate is used consistently with its labeling, the transient electrolyte changes that may occur do not result in medically important clinical adverse events.

Medical problems have arisen in patients taking oral sodium phosphate solution only when this OTC product was misused. For example, consumers sometimes mistakenly ingested an entire 240 mL bottle of sodium phosphate solution, instead of the 90 mL recommended dose. Consequently, the 240 mL bottle was taken off the market to prevent such misuse, but the 90 mL bottle is still marketed.

In this regard, it is notable that the case report by Campisi et al. that was cited by Dr. DiPalma in his letter indicates that sodium phosphate solution was used in a manner grossly inconsistent with the US professional labeling for this product. This misuse, which was not mentioned by Dr. DiPalma, almost certainly contributed to the problems of the surgical patient described in the case report.

InKine believes that Diacol would be far less likely to be misused than the OTC sodium phosphate solution, because InKine intends Diacol to be a prescription product that would be sold only in bottles that provide dosing for a single colon cleansing.

In his letter, Dr. DiPalma suggests that elderly patients with bone disease may be at increased risk from sodium phosphate bowel preparations. This suggestion appears to be based primarily on the Campisi report described above, regarding a single surgical patient in whom sodium phosphate solution was misused. Dr. DiPalma's suggestion is not

consistent with the available information regarding the safety of sodium phosphate, including data from the enclosed reproduction of a poster presentation. The poster was presented at the 1999 annual meeting of the American College of Gastroenterology, and describes InKine's two large, identical, investigator-blinded, controlled trials comparing

Diacol to Cherry Flavor NuLYTELY® in 845 patients undergoing colonoscopy. Notably, these trials had no exclusion criteria based on gender, advanced age, the presence of bone disease, or the use of medicines for the treatment or prevention of bone disease, as the poster indicates. While the poster states that "minor, transient" electrolyte shifts were reported in patients who took Diacol, they were "clinically insignificant," and, "In no case were clinical symptoms related to these electrolyte shifts." In addition, although we have no information on the age breakdown of the patients who have used the oral sodium phosphate solution in clinical practice over more than 100 years, it is probable that a million or more elderly patients (many with osteoporosis) have received this product as directed with no reported medically important clinical adverse events due to electrolyte changes.

The poster referenced above describes other important safety information from InKine's two large controlled trials. The poster indicates that in these studies, significantly fewer patients in the Diacol group reported the common purgative-associated adverse events of nausea, vomiting, and bloating, compared to NuLYTELY. There was no significant difference in the rate of the other common gastrointestinal symptom, abdominal pain, in the two studies combined. Sodium phosphate tablets, like sodium phosphate solution, are quite safe when used as directed.

As FDA is aware, Braintree has previously tried to disparage the safety of sodium phosphate products to the Agency and to physicians. Sadly, Dr. DiPalma's letter is consistent with this pattern of disparagement.

Thus, Dr. DiPalma's letter sheds no new light on the already settled issue of the safety of sodium phosphate, which is safe when used as directed. Sodium phosphate solution has been used for over 100 years in the US. We estimate that it has been taken by more than 10 million Americans as a bowel preparation. This vast experience indicates that when sodium phosphate is used consistently with its labeling, the transient electrolyte changes that may occur do not result in medically important clinical adverse events.

Second, we think it most regrettable that Dr. DiPalma failed to disclose in his letter his long and continuing history of close involvement with Braintree, the manufacturer of NuLYTELY and GoLYTELY®. A recent publication regarding a Braintree product by Dr DiPalma and others reveals that,

"Dr. DiPalma serves as a medical director/consultant to Braintree Laboratories ..." [3]

Dr. DiPalma's role as a medical director/consultant to Braintree raises a significant conflict of interest here because Braintree's products compete in the market with sodium phosphate bowel preparation products. Braintree would profit substantially if sodium phosphate products were no longer marketed in the US.

In addition, over the period from 1984 to 2000, Dr. DiPalma authored at least 13 published reports (including one on-line report) of investigations of the safety and efficacy of bowel preparations. [4] With one exception, all of the reported studies involved Braintree products. The sole exception was a clinical study (funded by Braintree) that dealt with a purported safety risk of a competing product. Of the 13 publications, only five included information regarding the source of support for the study. In all five cases, Braintree provided support for the study. In the other eight publications, the sources of support for the studies were not revealed. Also, FDA documents available to the public indicate that Dr. DiPalma was an investigator in at least one multicenter NDA study for a Braintree product that was performed prior to 1989. Thus, Dr. DiPalma has performed many studies for Braintree, consistent with his role as a medical director/consultant of that corporation.

Notably, Dr. DiPalma is listed in the 2000 Physician's Desk Reference (PDR) as the emergency medical contact for Braintree.

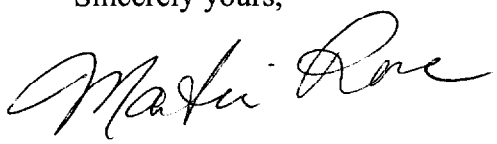
Dr. DiPalma wrote his letter to FDA on University of South Alabama stationery. His signature block included his academic title, but he never mentioned his many ties to Braintree or his role in the corporation. This gives the letter an air of academic impartiality and lack of pecuniary interest that is misleading. It was wrong for Dr. DiPalma not to reveal his relationship with Braintree. A simple statement like the one quoted above from his recent paper would have sufficed.

Three documents referenced above are enclosed and may be of interest to FDA. The first is a copy of Dr. DiPalma's recent paper in the American Journal of Gastroenterology that reveals his close ties to Braintree. The second is a copy of the first page of the 2000 PDR listing for Braintree products that indicates that he is Braintree's emergency medical contact. The third is a reproduction of the previously-cited peer-reviewed poster that was presented at the 1999 annual meeting of the American College of Gastroenterology. This poster describes the design and results of InKine's randomized, controlled, investigator-blinded studies comparing Diacol and Cherry Flavor NuLYTELY in patients undergoing colonoscopy. The authors of this poster conclude that compared to NuLYTELY, Diacol was "equivalent ... in the efficacy of colon cleansing"; "the incidence of the common gastrointestinal side effects of purgation, nausea, vomiting, and bloating were reported much less often in those patients who took Diacol"; and that Diacol was better accepted than NuLYTELY by patients in a variety of ways. The authors also conclude that Diacol use caused "minor, transient clinically insignificant electrolyte shifts, which self-corrected within 48 to 72 hours, more often than did

NuLYTELY." The results of these studies strongly support the safety and efficacy of Diacol Tablets as a colon cleansing agent.

Thank you for your consideration.

Sincerely yours,



Martin Rose, M.D., J.D.
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cc: Lilia Talarico, M.D. (HFD-180)
Charles Ganley, M.D. (HFD-560)
Cheryl Turner (HFD-560)

[1] 63 FR 27836, 27838 (May 21, 1998).
[2] Kolts BE. Letter. Am J Gastroenterology 1994;89:1119. The letter includes data from 1988 to 1994 regarding sales of sodium phosphate "kits" containing 45 mL bottles of sodium phosphate solution for oral use, but not for the 45 or 90 mL bottles sold separately. Clinical use of sodium phosphate has increased significantly since 1994. InKine is continuing to gather data on the use of oral sodium phosphate solution.
[3] DiPalma JA, DeRidder PH, Orlando RC, Kolts BE, Cleveland MvB. A randomized, placebo-controlled, multicenter study of the safety and efficacy of a new polyethylene glycol lavage. Am J Gastroenterology 2000;95:447-450. A copy of this publication is enclosed.
[4] Twelve of these were clinical studies and one was a veterinary study.

# ATTACHMENTS

1. **Journal Article**
2. **Copy of PDR Page**
3. **Poster Reproduction**